HEART REVIEW

Clinical appraisal of arterial stiffness: the Argonauts in front of the Golden Fleece

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Interest in evaluating arterial elastic properties has grown in parallel with the widespread availability of non-invasive methods for assessing arterial stiffness. A clinically useful diagnostic index must be pathophysiologically relevant, must be readily measurable, and must indicate the severity of the disease and predict the corresponding risk. Interventional modification of this index must parallel disease regression and benefit prognosis. The current evidence for the clinical value of estimating arterial stiffness (mainly of large, elastic-type arteries, such as the aorta and the carotids) in the contemporary era of cardiovascular medicine is reviewed.

Interest in evaluation of arterial elastic properties has grown impressively in recent years and in parallel with the widespread availability of non-invasive methods for assessment of arterial stiffness. In this article we discuss the current evidence for the clinical value of estimating arterial stiffness (mainly of large, elastic-type arteries, such as the aorta and the carotids) in the contemporary era of cardiovascular (CV) medicine. In this context, one has to keep in mind that the clinical importance of a diagnostic index or parameter (in our case, arterial stiffness) is established when some conditions are fulfilled. This index must (1) be pathophysiologically relevant; (2) be readily measurable with accurate and repeatable techniques; and (3) indicate the severity of disease and predict the corresponding risk. Lastly, the modification of this index by drugs or other interventions has to parallel disease regression and mediate a benefit in prognosis.

For purposes of simplicity in the present article, in the term arterial stiffness we often include wave reflections, as their timing is affected by arterial stiffness. These terms are not interchangeable, however, but they are equally important and complementary, as is emphasised in specific sections.

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IS THERE A SOLID PATHOPHYSIOLOGICAL BACKGROUND?

Stiffness is a dynamic component of arterial performance and it is susceptible to modification in both the short and the long term by several factors that affect the structure or function of the arterial wall.[1 2] Furthermore, stiffness is not distributed uniformly along the whole arterial network.

Several theoretical models have been proposed to describe the elastic behaviour of large arteries. According to the Windkessel model of circulation, the heart pumps blood periodically into a highly elastic component, the aorta, and then blood travels to the peripheral tissues through more or less inelastic conduits (muscular conduit arteries or resistance arteries). This model, although easy to understand, is not so realistic because it does not take into consideration either: (1) that arterial elasticity is not confined to the aorta but is spread over the other major arteries; or (2) that pressure waveforms differ in contour and amplitude along the arterial tree. Furthermore, this model does not take into account the existence of wave reflections in the circulation.[3]

In a more realistic model, the arterial tree is represented by a single distensible tube.[3] The heart pumps blood in at one end of this tube. The other end represents peripheral resistance. In this tube, cushioning and conduit properties are combined, but cushioning decreases progressively towards the periphery. The pulse wave generated by the left ventricle travels down the arterial tree and then is reflected at several peripheral sites.[4] Resistance arteries (small muscular arteries and arterioles) are the main reflecting sites of the periphery; however, these reflecting sites are not determined anatomically in a strict manner because they are subjected to structural and functional control. For example, the site of reflection is more central in the case of hypertension, atheromatous arteries or increased sympathetic activity. The velocity of the pulse wave is fast enough, so that the pulse generated by the left ventricle has adequate time within one cardiac cycle to travel to the periphery and then return. Thus, the pressure waveform recorded at any site of the arterial tree is the sum of the forward-travelling waveform generated by pump ejection and the backward travelling wave, the ''echo'' of the incident wave reflected at peripheral sites.[4] When the arteries are compliant and elastic, the reflected wave merges with the incident wave during diastole, thus augmenting the diastolic blood pressure and aiding coronary perfusion.[4] In contrast, when arteries are less compliant and are inelastic, pulse wave velocity increases, and both the incident and the reflected wave travel faster; thus, the reflected wave merges with the incident wave at systole and augments the systolic pressure. As a result, left ventricular afterload increases and

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CAD, coronary artery disease; CV, cardiovascular; HOPE, Heart Outcomes Prevention Evaluation; LIFE, Losartan Intervention For Endpoint reduction in hypertension

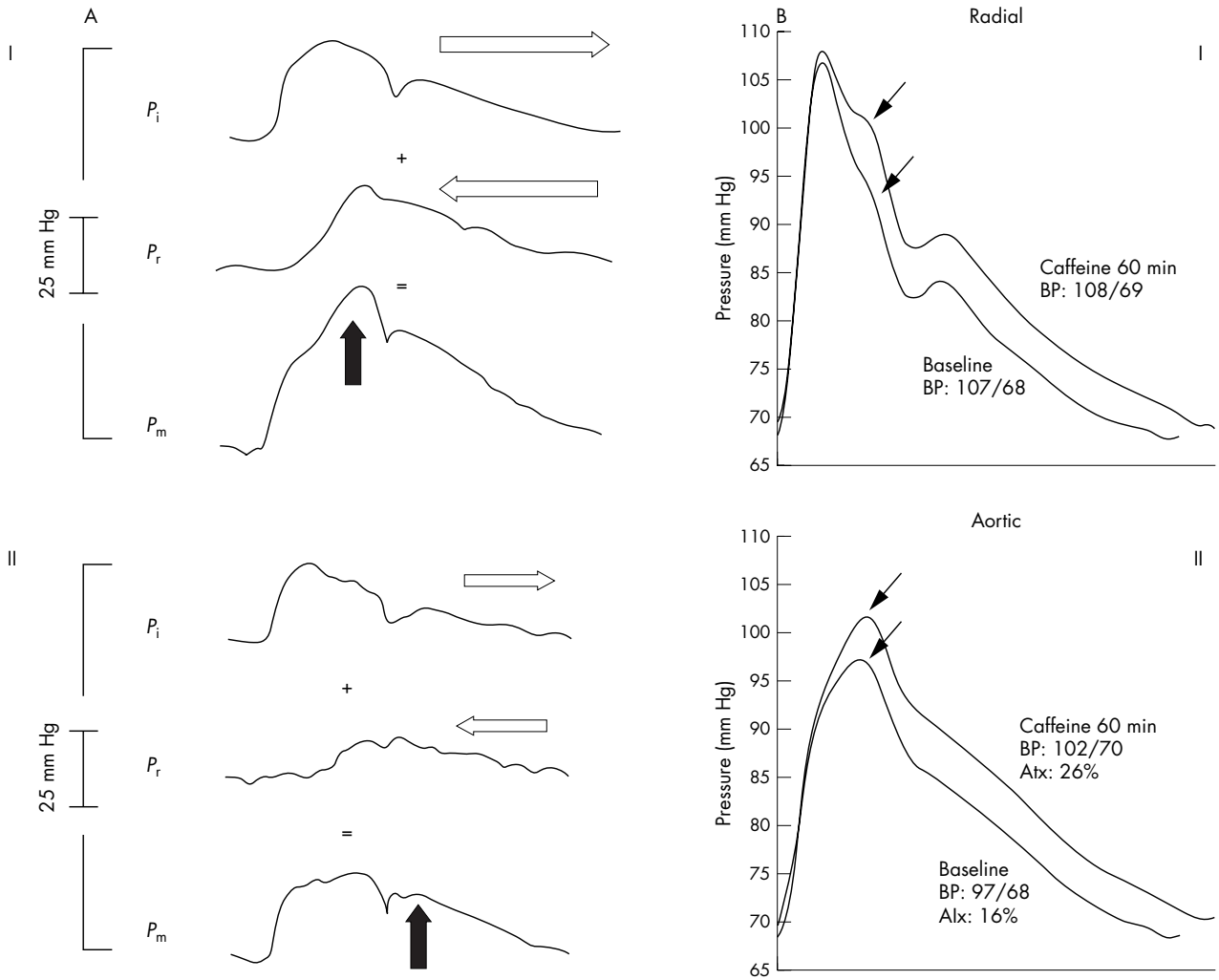

Figure 1 (A) Merged aortic pressure wave (Pm) and its components, incident (forward-travelling) wave (Pi) and reflected (backward-travelling) wave (Pr). In case of a stiff aorta or peripheral vasoconstriction (graph I), both Pi and Pr travel fast or the magnitude of the reflected wave is increased, thus augmenting the systolic pressure of Pm. Inverse phenomena occur in a distensible aorta or with vasodilatation (graph II). Length and thickness of white arrows correspond to the waveform velocity and the magnitude of the reflected wave, respectively, but are not to scale. Black arrows indicate point of merging of Pi and Pr. (B) The increase in the reflected wave (arrows) by caffeine does not affect peripheral peak systolic blood pressure (BP) (graph I). Because the reflected wave is added to a different point of the aortic waveform, however, it contributes to a rise in the central peak systolic pressure (graph II). Modified with permission from Yaginuma *et al*[5] (A) and Vlachopoulos *et al*[6] (B).

normal ventricular relaxation and coronary filling are compromised[4] (fig 1[5 6]). Apart from changes in the timing of the merging of the two waveforms, changes in the magnitude of the reflected wave may result from changes in the proportion of reflection owing to peripheral vasoconstriction[6] or, inversely, vasodilatation. In the context of this important functional coupling and interrelationship between heart and blood vessels, the notion of the ventricular–arterial stiffening as a coupling disease has long been proposed[4] and recently revived.[7]

In large elastic-type arteries, stiffness is mainly a function of the absolute and relative quantities of the major components of the extracellular arterial wall matrix, the collagen and elastin fibres.[2] The collagen to elastin ratio increases towards the periphery. Stiffness is also influenced by changes in the turnover of matrix proteins by metalloproteinases and other proteolytic enzymes. Moreover, it has been shown that vascular calcification is associated with increased large-artery stiffness.[8] Whereas in large, elastic-type arteries smooth muscle cells have a role, stiffness in smaller arteries, such as the muscular-type conduit and resistance arteries, is primarily determined by the bulk and contractility of the most abundant smooth muscle cells.[1 4] Recent evidence suggests that endothelium-derived compounds, mainly nitric oxide, may have a regulatory role in large-artery stiffness.[2]

Although the structural elements of the arterial wall have a prominent role in determining arterial stiffness, functional or haemodynamic parameters contribute as well. Stiffness of an artery changes in parallel with the distending pressure, given that more inelastic collagen fibres are recruited with increasing pressure.[4]

IS ARTERIAL STIFFNESS A MARKER OF DISEASE AND A PROGNOSTICATOR OF EVENTS?

A *marker* is a parameter or trait that is associated with the presence, the extent or the complications of a disease. On the other hand a *prognosticator* is related to the morbidity or mortality (that is, events) of this disease in the long term. There is now ample evidence that arterial stiffness is a marker of the severity of CV disease and predicts outcomes in the long term in several populations.

Arterial stiffness as a marker

In patients with essential hypertension, large-artery stiffness indicates the presence and extent of atherosclerotic disease and correlates with the CV risk as assessed by the Framingham risk score.[9] In the elderly, increased aortic stiffness is an independent marker of cognitive impairment.[10] In young patients with suspected coronary artery disease (CAD), increased wave reflections can separate patients with CAD from those without.[11] Wave reflections also correlate with CV risk in patients with atherosclerotic disease and interestingly enough they are indicative of the total risk even in apparently healthy people.[12]

Arterial stiffness as a prognosticator

Pulse pressure is the simplest index of arterial stiffness depending also on ventricular stroke volume. Although pulse pressure is not very accurate as an index of arterial stiffness, it is convenient on the basis of large population studies. The rise in pulse pressure with ageing or other conditions is mainly due to an increase both in large-artery stiffness and in the amount of the pulse wave that is reflected from the periphery.[4] Pulse pressure has been shown to be associated with all cause, CV and especially coronary mortality in asymptomatic men of low CV risk.[13] In the Framingham Study, pulse pressure was an independent predictor of CAD risk in middle-aged and elderly people without evidence of CV disease.[14]

Direct arterial stiffness and wave reflection indices were proved to have independent prognostic value. Historically, this was first shown in high-risk patient groups (end-stage renal disease), then in populations with risk factors (such as hypertension) or specific diseases (such as CAD), and then in more general population groups (elderly people). Aortic stiffness and wave reflections are strong independent prognosticators of all cause and especially CV mortality in patients with end-stage renal failure undergoing haemodialysis.[15 16] In patients with essential hypertension, large-artery stiffness predicts future coronary events, stroke,[17] and CV and all cause mortality.[18] In patients with CAD, aortic elastic properties and wave reflections are powerful and independent predictors of recurrent acute coronary events or death.[19 20] In older healthy people, aortic stiffness predicts the occurrence of CAD, stroke and total mortality.[21] The independent predictive value of aortic elastic properties is evident even in non-selected people older than 70 years.[22]

HOW EASY, ACCURATE AND REPRODUCIBLE ARE THE TECHNIQUES?

Several commercially available devices, which differ in the method of estimating stiffness and the arterial bed on target, have been developed. Central (aortic) pulse wave velocity is an established index of arterial stiffness, which can be measured non-invasively with high reproducibility. Additional important information mainly regarding central pressures and wave reflections is provided with analysis of the pulse waveform. In principle, from the non-invasively registered radial (or carotid) waveform, the central (aortic) waveform is synthesised with the use of transfer functions.[4] The study of aortic pulse wave velocity coupled with estimation of arterial wave reflections and central pressures therefore constitutes a more comprehensive and integrated approach to assessing arterial stiffness.

WHAT DETERMINES ARTERIAL STIFFNESS?

Table 1 lists the main demographic, clinical and lifestyle characteristics that influence arterial stiffness.

CV risk factors and diseases

Age is the main determinant of stiffness in large elastic arteries, independently of blood pressure or CV risk factors,[2 4] with a more pronounced increase after the age of 55 years. This is in part because of the degeneration and remodelling of the elastic components in the arterial wall with ageing.[4] At the cellular–molecular level, an age-related decrease in intracellular magnesium concentration has been independently associated with increases in stiffness. On the other hand, elastic properties of muscular arteries do not change significantly with increasing age.[4] Age-related arterial stiffening is similar for men and women, but arterial stiffness in women is usually a little lower than in men of the same age, and this has been related to sex hormone effects.

Most CV risk factors and diseases have an adverse effect on arterial stiffness. In essential hypertension elastic properties of large arteries are impaired: however, it is not agreed whether this reflects an alteration of the intrinsic elastic properties independently of blood pressure[23] or this is the passive effect of the increase in distending pressure.[24] Discrepancies may relate to the duration of hypertension, the age of the patients or the (segment of the) artery involved. In diabetic patients, stiffness of large arteries is found to be increased.[25] Hyperglycaemia and formation of advanced glycation end products, with subsequent cross linking of collagen, are perhaps pathophysiologically associated with a reduction of arterial elasticity. Interestingly, stiffness increases even in glucose-intolerant patients[25] or in people with family history of diabetes. In the light of data

Table 1 Demographic, clinical and lifestyle determinants of arterial elastic properties

Age
Sex
Cardiovascular diseases and disorders
Hypertension
Coronary artery disease
Peripheral artery disease
Heart failure
Cardiac syndrome X
Endothelial dysfunction
Endocrinological and metabolic diseases
Diabetes mellitus
Impaired glucose tolerance
Dyslipidaemias
Metabolic syndrome
Hyperhomocysteinaemia
Hypothyroidism
Nutritional and lifestyle aspects
High sodium chloride consumption
Obesity
Smoking
Coffee, caffeine
Chronic alcohol consumption
Sedentary lifestyle
Resistance training
Genetic variants
Genes of the RAAS
AT1 polymorphism
ACE polymorphism
Aldosterone synthase polymorphism
Angiotensinogen polymorphism
Genes of the extracellular matrix proteins
Elastin
Fibrillin 1
Matrix metalloproteinases
Gynaecological conditions and disorders
Menopause
Pre-eclampsia
Polycystic ovaries syndrome
Other
Inflammation
Acute inflammation
Chronic inflammatory diseases
Subclinical, low-grade inflammation
End-stage renal disease
Family history of atherosclerotic disease
Sleep apnoea syndrome

ACE indicates angiotensin converting enzyme; AT1, angiotensin receptor type 1; RAAS, renin–angiotensin–aldosterone system.

showing that physiological insulin concentrations may have beneficial effects in arterial elastic properties, and that the metabolic syndrome is independently associated with large-artery stiffness,[26] a new link between insulin resistance and increased stiffness is established. Although aortic distensibility has been found paradoxically to be increased in young patients with early-stage dyslipidaemias, these disorders are generally associated with an impairment of large-artery elasticity in later stages of such syndromes.

In CAD, aortic stiffness is increased and wave reflections are enhanced.[10 27] These changes may further compromise the perfusion through a stenotic coronary artery during the diastolic period.[4 6] Interestingly, increased stiffness has been observed even in patients with cardiac syndrome X. In patients with heart failure the elastic properties of the large and medium-sized arteries are impaired, and this is mainly associated with endothelial dysfunction and increased sympathetic activity. In end-stage renal disease stiffening is more pronounced in the aorta than in the peripheral arteries.[15 16]

Genetic background

Genetic factors not taken into account in the risk estimation with the classic CV risk factors may also contribute to arterial stiffening. Interestingly, arterial elastic properties are impaired in young people with a family history of hypertension, diabetes or myocardial infarction.[28] Specific polymorphisms have been related to increased arterial stiffness.[29] Furthermore, recent studies showed that measures of stiffness and components of blood pressure are linked to specific genetic loci in human chromosomes.[30]

Lifestyle characteristics

Lifestyle characteristics are important determinants of arterial stiffness. Cigarette smoking,[31 32] passive smoking[33] and cigar smoking[34] have an adverse impact on the elastic properties of large and medium-sized arteries. Although cigarette smoking is an established CV risk factor, however, the effect of long term smoking on arterial stiffness has not been defined. Short[5 35] and long term[36] intake of caffeine have an unfavourable effect on arterial performance. Interestingly, cigarette and caffeine have synergistic adverse effects on arterial elasticity when a person is concurrently exposed to their effects.[29] Obesity, weight gain and high dietary intake of sodium chloride may aggravate arterial stiffness.[2 37 38] Moreover, the level of physical activity has a prominent role and sedentary people are known to have increased stiffness compared with people who exercise regularly.[2]

Inflammation

In chronic inflammatory diseases such as lupus erythematosus or rheumatoid arthritis, arterial stiffness is increased independently of the presence of atherosclerosis.[39 40] Importantly, chronic low-grade subclinical inflammation is a common denominator of most CV risk factors, diseases and lifestyle characteristics. This subclinical inflammation as indicated by high-sensitivity C reactive protein has been positively related to measures of wave reflections and stiffness in apparently healthy people and in the general population.[41 42] Moreover, we have recently shown that even an acute, mild, transient inflammatory stimulus generated by *Salmonella typhi* vaccine may lead to deterioration of large-artery stiffness, thus establishing a cause and effect relationship[43] (fig 2). This finding is clinically relevant and may comprise the pathophysiological background of the association between an acute inflammatory disorder and the increased short-term risk of a CV event.

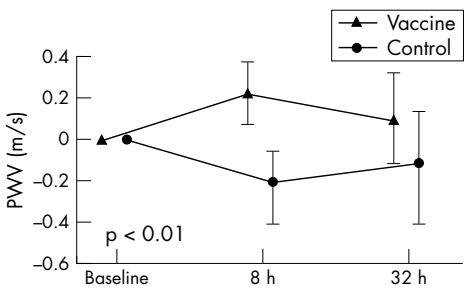

Figure 2 Increase in carotid–femoral pulse wave velocity (PWV) induced by a mild, transient systemic inflammation that is generated by *Salmonella typhi* vaccine (dots indicate changes from baseline). Modified with permission from Vlachopoulos *et al*.[43]

HOW CAN ARTERIAL STIFFNESS BE IMPROVED?

An increasing number of strategies, including dietary and lifestyle modifications as well as several pharmacological treatments, have proved beneficial in reducing arterial stiffness[1 2 7] (table 2). Although many of these interventions may also have a beneficial impact on prognosis, evidence is insufficient that the improvement of arterial elastic properties per se may account for this benefit. This is mainly due to the concurrent favourable modification of other parameters and risk factors (such as blood pressure, blood lipids or glucose concentrations) by such interventions. So far only one study has shown that a favourable change in arterial stiffness may confer an independent benefit on survival.[44] Large, longitudinal controlled trials are therefore needed to unravel whether the benefit of a de-stiffening intervention is in part due to improved elasticity of the arterial wall per se.

Dietary and lifestyle modifications

Several dietary modifications are efficient in reducing stiffness. Flavonoids are substances that may increase endothelial nitric oxide availability both directly (by upregulating nitric oxide synthase) and indirectly (through their antioxidant action). They are abundant in fruits, vegetables and several other plant products. It has been shown that a flavonoid-rich diet may reduce arterial stiffness in middle-aged and elderly people.[45] Also, we have recently shown that

Table 2 Interventions that improve arterial stiffness

Drugs
Hypertension drugs
ACE inhibitors
AT1 antagonists
Calcium channel blockers
β blockers (with vasodilating properties)
Diuretics
Nitrates
Diabetes drugs
Thiazolidinediones (eg, rosiglitazone)
Statins
Aldosterone antagonists (eg, spironolactone)
Folic acid
Phosphodiesterase type 5 inhibitors (sildenafil)
AGE formation blockers or cross-link breakers
Dietary modifications
High flavonoid intake
Dark chocolate
Fruits and vegetables
Soya beans
Moderate alcohol consumption
Dietary salt restriction
Polyunsaturated fatty acid, fish oil
Garlic
Other
Aerobic training
Weight loss

ACE, angiotensin converting enzyme; AGE, advanced glycation end products; AT1, angiotensin II receptor type 1.

dark chocolate rich in procyanidins (a subclass of flavonoids) in the short term reduces wave reflections in young healthy adults, independently of changes in blood pressure.[46]

Moderate alcohol consumption has a beneficial impact on arterial elasticity. In line with the J-shaped association between alcohol intake and large-artery stiffness, people who consume 4–10 glasses of alcoholic beverages a week benefit the most.[47]

Restriction of dietary sodium intake also has a beneficial effect on arterial compliance.[2] Blood pressure reduction does not account for all the amount of this improvement, which is also mediated in part by a beneficial change in the arterial wall structure.

Although weight loss in general has a beneficial effect on arterial elasticity, it was initially believed that the effect is mediated by the concurrent reduction in blood pressure. Only recently has the independent beneficial effect of weight loss on large-artery elasticity been unravelled.[38]

Regular aerobic exercise (such as walking, jogging or swimming) may decelerate the age-related increase in large-artery stiffness or even reverse it, but not all types of exercise are beneficial, given that high-intensity resistance (muscle strengthening) training exerts a detrimental stiffening effect on the arterial tree.[2 48 49]

Pharmacological interventions

Several classes of hypertension drugs are effective in reducing arterial stiffness.[1] This is expected, given that blood pressure reduction per se unloads the stiff components of the arterial wall, such as collagen. Beyond this functional improvement in stiffness shared by most hypertension drugs, some of them may further benefit stiffness by favouring a de-stiffening remodelling of the arterial wall, such as reducing the collagen content, increasing the elastin to collagen ratio or changing the spatial arrangement of the wall fibres.[1 2] Drugs acting on the renin–angiotensin–aldosterone axis, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, have been shown to improve stiffness in several clinical settings.[1 2 7] Moreover, aldosterone antagonists (such as spironolactone) induce a beneficial remodelling of the arterial wall.[2 7] Calcium channel blockers[1 23] and vasodilating β blockers (such as nebivolol or celiprolol) also have a favourable effect on arterial elasticity.[1]

Although nitrates are not used as pure hypertension drugs, they reduce wave reflections after short term administration.[1] New nitric oxide donors also appear to be promising. Furthermore, phosphodiesterase type 5 inhibitors (sildenafil) have been shown to reduce arterial stiffness and wave reflections in patients with CAD or heart failure.[50 51]

Statins reduce arterial stiffness in patients with[2] and without[52] dyslipidaemia, suggesting a benefit in the intrinsic properties of the arterial wall.

The beneficial effect of antioxidant drugs such as ascorbic acid is debated, although there are some scarce data that it may decrease arterial stiffness in specific populations.

There are some indications that other drugs, such as diabetes drugs that activate the peroxisome proliferator-activated receptor γ (thiazolidinediones), oestrogen replacement therapy, oestrogen receptor modulators (raloxifene), folic acid and drugs that block the formation or cleave the cross links of advanced glycation end products, such as aminoguanidine and ALT-711, beneficially alter arterial elastic properties in preliminary studies.[2] The clinical significance of these effects, however, remains to be determined.

CENTRAL OR PERIPHERAL PRESSURE: WHICH IS MORE IMPORTANT?

Normally, the amplitude of the pressure waveform increases from the aorta towards the periphery (amplification).[4] This is particularly true in younger people, resulting in a discrepancy between the measured blood pressure in the brachial artery and the actual pressure in the aorta. In older people this discrepancy is reduced because early wave reflections increase central systolic pressure. An exaggeration of the phenomenon of amplification is pseudohypertension, in which systolic brachial blood pressure is raised in young, usually tall people with very elastic arteries, but their central systolic pressure is normal.[53 54]

Central (aortic) pressures are the ones that are physiologically significant. Indeed, it is the aortic systolic pressure that the left ventricle must cope with during systole (afterload). Moreover, aortic diastolic pressure is the one that determines coronary filling. Furthermore, the distending pressure in the central arteries is very important because these elastic arteries (aorta, carotid) are the predominantly affected ones, and they degenerate with ageing and in hypertension, in contrast to the less affected muscular peripheral arteries such as the brachial and the radial.[4] Importantly, central and not brachial pulse pressure is a predictor of mortality in patients with end-stage renal disease,[55] as well as a determinant of intima–media thickness in the carotid arteries[56] and of ascending aorta diameter in patients with Marfan's syndrome.[57]

The effect of interventions on aortic pressures may not be evident by pressure measurements in the periphery because the reflected wave is added to a different part of each waveform (central, peripheral; fig 1B).[5 35] This may explain (together with the effect at the tissue level) why in large-scale trials, such as the HOPE (Heart Outcomes Prevention Evaluation) and LIFE (Losartan Intervention For Endpoint reduction in hypertension) studies or the very recent ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), the observed clinical benefit was greater than that expected according to the decrease in peripheral blood pressure. Indeed, for example, only ramipril decreases wave reflections, whereas atenolol has the opposite effect.[58] Importantly, the recently published CAFÉ (Conduit Artery Function Evaluation) Study,[59] an ASCOT Substudy, showed that a change of central but not peripheral blood pressure with hypertension treatment is an independent determinant of clinical outcomes.

ASSESSMENT OF ARTERIAL STIFFNESS IN THE CLINICAL SETTING

"Arterial age" is a concept that reflects the risk conveyed by the status of the large arteries and integrates the effect of known and (currently) unknown risk factors. Arterial ageing may be different from chronological ageing and is determined by the effect of both the genetic background and environmental factors on arterial elastic properties. Stiffening of the arteries can be regarded as target organ damage and this notion is shared by the last European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension, which recommend the measurement of pulse wave velocity and wave reflection indices for detecting vascular damage.[60] In practical terms, this means that patients can be re-stratified to a different risk category according to the arterial age with a view towards more aggressive treatment in case of raised risk. This may be particularly important for patients with accelerated arterial ageing not expected by conventional risk factors. Furthermore, in patient groups such as those with hypertension or dyslipidaemia, changes of arterial stiffness and wave reflection indices can reflect the effectiveness of treatment, in addition to changes of (peripheral) blood pressure or blood lipids. Lastly, estimation of arterial stiffness and central pressures may serve as an auxiliary diagnostic tool, such as in pseudohypertension of youth.

ISSUES REMAINING TO BE RESOLVED

Present techniques of assessment are largely accurate and reproducible; however, evolution and refinement are always

welcome. Clearly, studies that will prove that ''treating'' arterial stiffness confers an additional benefit in prognosis on top of other effects of treatment are needed before arterial de-stiffening is identified as an independent therapeutic target. To this end, large-scale studies with arterial stiffness as a secondary end point are under way, but more are needed. Furthermore, establishment of normal values and cut-off points is of the utmost importance and studies such as the recently published ACCT (Anglo-Cardiff Collaborative Trial)[61] are very helpful for this purpose.

The clinical implementation of arterial stiffness assessment has long been the Golden Fleece for the Argonauts of arterial function. Colchis is on the horizon.

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IMAGES IN CARDIOLOGY

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Mycotic aneurysm complicating prosthetic valve endocarditis

A 62-year-old man underwent aortic xenograft valve replacement for treatment of severe congenital aortic valve stenosis. Nine months later the patient was admitted to a community hospital with recurrent fever. Blood cultures grew *Candida albicans* and an echocardiogram showed fine granular vegetations on the prosthetic valve leading to the diagnosis of candida endocarditis. Under standard antifungal treatment symptoms resolved quickly and the patient was discharged on oral fluconazole. Two months later he was admitted to our centre with new onset fever and an acute insult of the left middle cerebral artery with temporary motor aphasia and paresis of his right arm. A broad focus search including cranial, thoracic and abdominal computer tomographic (CT) scans remained unrevealing. High dose antifungal treatment including amphotericin B and flucytosin did not lead to clinical improvement. Finally, the graft was surgically replaced. However, despite ongoing antifungal treatment fever did not recess. We performed a leucocyte scintigram revealing an inflammatory process in the left knee. Physical examination of the knee showed no abnormalities. A subsequent magnetic resonance tomogram and femoral angiogram corroborated the diagnosis of a popliteal mycotic aneurysm. After surgical removal of the aneurysm the patient quickly recovered and has been symptom-free for the last two years. This case demonstrates that mycotic aneurysms are serious, but rarely considered, complications of fungal prosthetic valve endocarditis and highlights the potential value of a leucocyte scintigram as part of an extended investigation.

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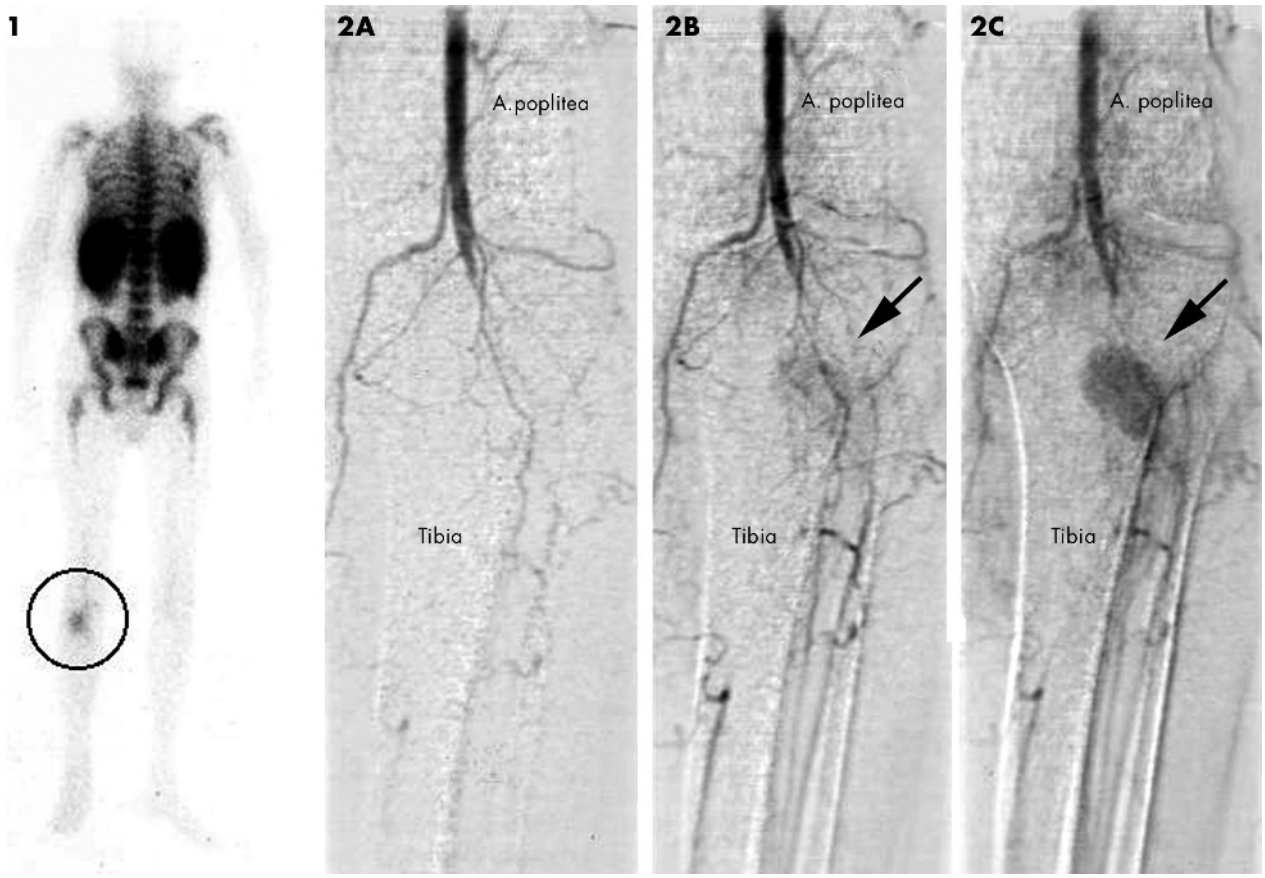

(1) Leucocyte scintigram revealing an inflammatory process in the left knee (circle). (2A–C) Sequential images of a digital subtraction angiogram of the femoral artery. Upon injection of contrast agent an occlusion of the popliteal artery is revealed. A few seconds later a round contrast filled aneurysm appears (arrows).